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● *Review Article*

GUIDELINES AND GOOD CLINICAL PRACTICE RECOMMENDATIONS FOR CONTRAST-ENHANCED ULTRASOUND (CEUS) IN THE LIVER–UPDATE 2020 WFUMB IN COOPERATION WITH EFSUMB, AFSUMB, AIUM, AND FLAUS

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Abstract—The present, updated document describes the fourth iteration of recommendations for the hepatic use of contrast-enhanced ultrasound, first initiated in 2004 by the European Federation of Societies for Ultrasound in Medicine and Biology. The previous updated editions of the guidelines reflected changes in the available contrast agents and updated the guidelines not only for hepatic but also for non-hepatic applications. The 2012 guideline requires updating as, previously, the differences in the contrast agents were not precisely described and the differences in contrast phases as well as handling were not clearly indicated. In addition, more evidence has been published for all contrast agents. The update also reflects the most recent developments in contrast agents, including U.S. Food and Drug Administration approval and the extensive Asian experience, to produce a truly international perspective. These guidelines and recommendations provide general advice on the use of ultrasound contrast agents (UCAs) and are intended to create standard protocols for the use and administration of UCAs in liver applications on an international basis to improve the management of patients. (E-mail: c.f. dietrich@googlemail.com)

Key Words: **Contrast-enhanced ultrasound, World Federation for Ultrasound in Medicine and Biology, Guideline, Liver.**

INTRODUCTION

The present, updated document describes the fourth iteration of recommendations for the hepatic use of contrast-enhanced ultrasound (CEUS), which was initiated by the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) (Albrecht et al. 2004). The previous updated editions of the guidelines reflected changes in the available ultrasound contrast agents (UCAs) and updated the guidelines for not only hepatic but also non-hepatic applications (Claudon et al. 2013a, 2013b; Sidhu et al. 2018a, 2018b).

The 2012 guideline requires updating, as previously the differences in contrast agents were not precisely described, evidence-based recommendations were not given and differences in contrast phases as well as handling were not clearly indicated. In addition, more evidence has been published for all contrast agents. This update also reflects the most recent developments in contrast agents, including U.S. Food and Drug Administration (FDA) approval and extensive Asian experience, to produce a truly international perspective.

The requirement for worldwide guidelines on the use of CEUS in the liver instigated the World Federation for Ultrasound in Medicine and Biology (WFUMB) to facilitate discussions, in conjunction with its component federations, namely, the Asian Federation of Societies for Ultrasound in Medicine and Biology (AFSUMB), American Institute of Ultrasound in Medicine (AIUM), Australasian Society for Ultrasound in Medicine (ASUM), Federation of Latin America Ultrasound (FLAUS), and EFSUMB and in collaboration with the International Contrast Ultrasound Society (ICUS), to bring the 2012 liver guidelines up-to-date, recognizing the fact that UCAs are now licensed in increasing parts of the world. Of the 38 authors, 19 were from nine European countries representing EFSUMB; 13 from China, Japan, Korea and India representing AFSUMB; 5 from the United States representing AIUM; and 1 from MASU and FLAUS.

As for the previous guidelines, this document is based on comprehensive literature surveys, including results from prospective clinical trials. We followed an EFSUMB Policy Document on development strategy for clinical practice guidelines, position statements and technological reviews adopted by WFUMB (Jenssen et al. 2019). For each key topic, the authors performed a systematic literature search based on an explicit search strategy using Medline, Cochrane library and, if appropriate, further defined databases/sources. The search strategy was pre-defined with respect to sources (*e.g.,* Medline), inclusion criteria (*e.g.,* language of the publication, time period, study type, full publication), exclusion criteria and search terms. The evidence used to substantiate recommendations was summarized in evidence tables including information on study type (*e.g.,* systematic review and meta-analysis, randomized control trial, prospective/retrospective cohort study with defined outcome parameters, case series), case numbers, important outcomes and limitations. On topics for which

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no significant study data were available, evidence was obtained from expert committee reports or was based on the consensus of experts in the fields of ultrasound (US) and CEUS during the consensus conferences. Recommendations were prepared in task force groups and finally discussed and voted on in a meeting of CEUS experts held in Granada in June 2019. Level of evidence (LoE) was assigned to recommendations based on evidence tables.

This joint effort has again resulted in simultaneous publication in the official journals of WFUMB and EFSUMB (*i.e., Ultrasound in Medicine and Biology* and *Ultraschall in der Medizin/European Journal of Ultrasound*).

These guidelines and recommendations provide general advice on the use of UCAs. They are intended to create standard protocols for the use and administration of UCAs in liver applications on an international basis and to improve the management of patients. Individual cases must be managed on the basis of all clinical data available.

WORLDWIDE COMMERCIAL AVAILABILITY OF UCAS

Availability of UCAs for clinical use is based on the approval by regulatory agencies specific to the territory of intended use. Currently, four agents are available internationally for use in the liver, listed here with their manufacturers.

- Definity/Luminity (Lantheus Medical Imaging, Inc., North Billerica, MA, USA)
- SonoVue/Lumason (Bracco Suisse SA, Geneva, Switzerland)
- Optison (GE Healthcare AS, Oslo, Norway)
- Sonazoid (GE Healthcare AS, Oslo, Norway)

The approval of these agents varies throughout the world along with the approved indications. ICUS in collaboration with WFUMB has developed an interactive map (Fig. 1).

INDICATIONS, CONTRAINDICATIONS, SAFETY CONSIDERATIONS

The indications and contraindications differ among different UCAs; detailed information can be found in the official package inserts of the drugs.

Safety considerations

UCAs can be administered safely in various applications with minimal risk to patients (Piscaglia and Bolondi 2006; Main et al. 2007, 2009; Dietrich et al. 2017; Tang et al. 2017; Sidhu et al. 2018a). They are not excreted through the kidneys and can be administered to patients with renal insufficiency with no risk of contrast-related nephropathy or nephrogenic systemic fibrosis. There is no additional need for biochemical assessment or fasting before injection, and there is no evidence of any effect on thyroid function, as UCAs do not contain iodine (Claudon et al. 2013a, 2013b). UCAs have a very low rate of anaphylactoid-type reactions (1/7000 patients, corresponding to 14/100,000 or 0.014%) (Kitzman et al. 2000; Piscaglia and Bolondi 2006; Wilson and Burns 2010; Tang et al. 2017), significantly lower than the rate for current iodinated computed tomography (CT) agents (35−95/100,000 patients, 0.035%−0.095%) (Cochran et al. 2001) and anaphylactoid reactions associated with gadolinium-based contrast agents (4/64 (6.3%) (Hunt et al. 2009). Serious anaphylactoid-type reactions to UCAs are observed in approximately 1 in 10,000 exposures (0.01%) (Tang et al. 2017; Sidhu et al. 2018b).

SonoVue data pooled from 75 completed studies (of 6307 patients) in Europe, North America and Asia revealed that the most frequent adverse events were headache (2.1%), nausea (0.9%), chest pain (0.8%) and chest discomfort (0.5%). All other adverse events occurred at a frequency of less than 0.5% (Committee for Medicinal Products for Human Use 2014). Most adverse events were mild and resolved spontaneously within a short time without sequelae. Most cases of allergy-like events and hypotension occurred within a few minutes after injection of the agent. The overall reported rate of fatalities attributed to SonoVue is low (14/2,447,083 exposed patients, 0.0006%) and compares favorably with the risk for fatal events reported for iodinated contrast agents (approximately 0.001%). In all reported fatalities after use of an UCA, in both cardiac and non-cardiac cases, an underlying patient medical circumstance played a major role in the fatal outcome.

The intravesical administration of UCAs has been evaluated in a total of 7082 children described in 15 studies and in a European survey of 4131 children, 0.8% of whom reported adverse events, mostly related to bladder catheterization (Darge et al. 2013; Papadopoulou et al. 2014). Intravenous CEUS is also used in the pediatric population (Sidhu et al. 2017) and in numerous other documented areas (Sidhu et al. 2018b). The FDA recently approved the use of Lumason for pediatric liver imaging (Sidhu et al. 2017b), which is an important development. This application is, however, still off label in pediatric imaging in many countries. A significant reduction in exposure to ionizing radiation is likely to be achieved in many areas by using CEUS in pediatric patients (Sellars et al. 2014; Sidhu et al. 2017).

Most recently it was reported that the use of SonoVue appears to be safe in pregnant women (Schwarze et al. 2020).

Recommendation 1. Intravenous use of UCAs in adult populations is safe. (LoE 2) (Pro 28, Against 0, Abstain 0)

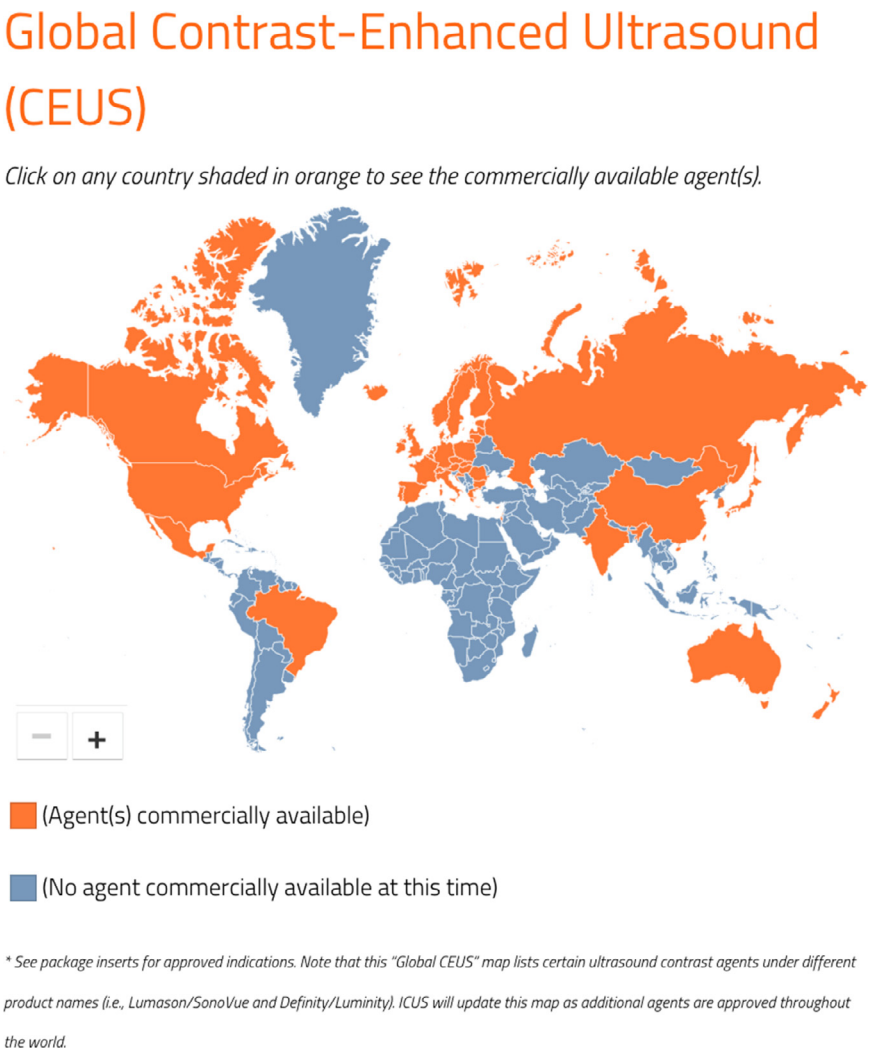

Fig. 1. Approval status of ultrasound contrast agents. The International Contrast Ultrasound Society (ICUS) in collaboration with the World Federation for Ultrasound in Medicine and Biology (WFUMB) has developed an interactive map on the approval status of contrast agents. An updated version of this map can be found online. (http://icus-society.org)

Recommendation 2. Intravenous use of UCAs in pediatric populations is safe. (LoE 3) (Pro 28, Against 0, Abstain 0)

Recommendation 3. Intracavitary use of UCAs is safe. (LoE 2) (Pro 27, Against 0, Abstain 1).

LIVER CEUS: SCANNING TECHNIQUE AND BASIC IMAGE INTERPRETATION

The study procedure is well documented in previous CEUS guidelines (Claudon et al. 2013a, 2013b) and has been described in detail in a recent WFUMB position paper (Dietrich et al. 2018b). Before performing a liver CEUS study, it is necessary to review the patient's clinical history, laboratory data and any prior imaging findings (Claudon et al. 2013a, 2013b).

Study procedure

Before CEUS, cysts and calcifications must be identified by conventional US because these structures do not exhibit contrast enhancement and could therefore be erroneously interpreted as a malignant infiltration if only scanned in the late phase (LP). When cysts are missed by the baseline examination, it is necessary to carefully review both the contrast and reference images and to analyze the B-mode pattern of the liver tissue after the disappearance of the microbubbles.

Interpretation

CEUS of the liver has three overlapping vascular phases after the injection of UCA because of the dual

Table 1. Vascular phases in contrast-enhanced ultrasound of the liver (visualization post-injection time).

Phase	Start (s)	End (s)
Arterial	10−20	30−45
Portal venous	30−45	120
Late	>120	Bubble disappearance (approximately 4−8 min)
Post-vascular	>8 min	Approximately 30 min

blood supply of the liver, that is, hepatic artery and portal vein (respectively 25%−30% and 70%−75% of liver blood flow in non-cirrhotic conditions) (Table 1).

- The *arterial phase* (AP) provides information on the degree and pattern of the arterial vascular supply of a focal liver lesion (FLL). Early arterial enhancement pattern and vascular architecture are best seen in slow replay of a stored cine loop.
- The *portal venous phase* (PVP) represents the arrival of UCA through the portal system, resulting in diffuse and maximal enhancement of normal liver parenchyma.
- The *late phase* (LP) lasts until clearance of the UCA from the circulation and depends on the type and dose of UCA, total scanning time, acoustic power output and sensitivity of the US system.
- The post-vascular phase is observed only with Sonazoid and represents uptake of the UCA by phagocytotic cells (*e.g.,* Kupffer cells).

Slight/moderate variations of timing may occur, particularly in the case of cardiac dysfunction and in patients with vascular liver disease.

Vascular architecture and phase-specific contrast enhancement of the lesion compared with the adjacent liver parenchyma are the most important diagnostic features for the characterization of FLLs (Claudon et al. 2013a, 2013b).

DIFFERENCES BETWEEN CEUS AND OTHER CONTRAST-ENHANCED IMAGING MODALITIES (CONTRAST-ENHANCED COMPUTED TOMOGRAPHY [CECT], CONTRAST-ENHANCED MAGNETIC RESONANCE IMAGING [CEMRI])

UCAs comprise gas-filled particles (microbubbles), differ in fundamental respects from the agents used in CECT and CEMRI and, for this reason, play a complementary problem-solving role for indeterminate FLLs. Unlike CT and MR agents, microbubbles are not excreted by the kidneys. With the exception of Sonazoid, UCAs are purely intravascular agents. Therefore, CEUS should be considered as the first contrast imaging modality in patients with renal insufficiency. UCAs can be safely administered more than once during the same examination. While the dynamic phases of liver enhancement with UCA resemble those of CECT with iodinated agents and CEMRI with gadolinium chelates, imaging is real time with US. Other important differences exist and are well described in the literature (Faccioli et al. 2007; Wilson et al. 2007; Rossi et al. 2008; D'Onofrio et al. 2015). For FLL characterization, an overall improvement in sensitivity and specificity is found for CEUS compared with CECT (Quaia et al. 2004; Seitz et al. 2009; Trillaud et al. 2009; Friedrich-Rust et al. 2013; D'Onofrio et al. 2014; Barr 2018). CEUS, in addition, is reported to be invaluable in providing characterization of indeterminate FLLs on CT, magnetic resonance imaging (MRI) and positron emission tomography (Burns and Wilson 2007; Laghi et al. 2010; Parsai et al. 2019). It is also reported that CEUS should be the subsequent imaging modality for all CT- and MR-indeterminate nodules before biopsy is undertaken (Jo et al. 2017).

Recommendation 4. CEUS is recommended in patients with inconclusive findings at CT or MR imaging. (LoE 2, strong recommendation) (Pro 30, Against 1, Abstain 0)

Recommendation 5. CEUS should be considered as the first contrast imaging modality in patients with renal insufficiency. (LoE 5, strong recommendation) (Pro 31, Against 0, Abstain 0)

DETECTION OF MALIGNANT FLLS: TRANSABDOMINAL APPROACH

Conventional US is the most frequently used modality for the primary imaging of abdominal organs, including the liver, but is less sensitive in the detection of FLLs than CECT, CEMRI or intra-operative US. A number of studies (Konopke et al. 2005, 2007; Dietrich et al. 2006; Quaia et al. 2006; Larsen et al. 2007, 2009; Piscaglia et al. 2007; Cantisani et al. 2010; Muhi et al. 2011; Itabashi et al. 2014) have reported that CEUS has a considerably higher sensitivity of up to 80%−90% in detecting liver metastases, comparable with those of CECT (Larsen 2010) and CEMRI (Cantisani et al. 2010). Furthermore, some reports have indicated that CEUS is of particular usefulness with metastases ≤10 mm (Forner et al. 2008; Dong et al. 2017). CEUS has dramatically increased the capability of US to detect FLLs and has the potential to be incorporated into the diagnostic algorithm for malignant FLLs.

Study procedures

The study procedure is described above. A second contrast administration (re-injection technique) can be used to confirm the metastatic nature of focal areas of contrast washout by demonstrating (secondary) AP enhancement within the areas of contrast washout.

Detection of metastatic lesions

The typical and almost invariable appearance of metastases is focal contrast washout. The enhancement patterns observed during the AP have limited clinical utility in lesion detection (Claudon et al. 2013a, 2013b; Dietrich et al. 2018c).

With vascular phase agents (SonoVue/Lumason, Definity/Luminity, Optison), several studies have reported that the accuracy of detection of liver metastases is comparable with those of CECT and CEMRI, when scanning conditions allow complete imaging of all liver segments (Larsen et al. 2007). However, it should be noted that most of the studies have used initial and/or follow-up imaging (mostly CT examinations and sometimes MRI, and intra-operative US) as a reference standard, and very few reports include histologic or pathologic confirmation. Nonetheless, as CT and MRI are currently the modalities of choice for metastatic FLL detection, comparison of CEUS with these techniques seems reasonable in evaluating the diagnostic efficacy of CEUS. In addition, histologic confirmation of every malignant FLL in patients with clear imaging diagnosis might not be ethically appropriate. According to a meta-analysis including 828 metastases from 18 studies, the overall sensitivity of CEUS for diagnosis of metastases was 91% (95% confidence interval [CI]: 87%−95%) (Friedrich-Rust et al. 2013).

Recommendation 6. CEUS can be used for liver metastasis detection as part of a multimodality imaging approach. (LoE 2, weak recommendation) (Pro 31, Against 0, Abstain 0)

Detection of HCCs and intrahepatic cholangiocellular carcinoma (ICC)

With all UCAs, most hepatocellular carcinomas (HCCs) exhibit AP hyper-enhancement (APHE), but the short duration of APHE makes adequate assessment of the whole liver impracticable. The LP lasts long enough for a detailed examination, but the appearance of HCC varies. Importantly, not all HCCs exhibit contrast washout in the LP, limiting the sensitivity of CEUS for HCC detection. CEUS is not recommended for staging of HCCs except for patients with a portal vein tumor thrombus (Tang et al. 2018; Wilson et al. 2018).

With the post-vascular phase UCA (Sonazoid), scanning the entire liver ≥10 min after injection helps to detect malignant nodules, as the typical HCC appears as an enhancement defect (Karhunen 1986; Hatanaka et al. 2008; Maruyama et al. 2009; Moriyasu and Itoh 2009; Guang et al. 2011; Martie et al. 2012). However, approximately half of well-differentiated HCCs do not exhibit enhancement defects in the post-vascular phase (Arita et al. 2011a).

ICCs behave in virtually the same manner as metastases, washing out rapidly and appearing as defects in the LP, regardless of their appearance in the AP (Xu et al. 2006). This pattern may facilitate detection of satellite nodules adjacent to a larger lesion that were not visualized on conventional US.

Recommendation 7. Routine use of CEUS for the surveillance of patients at risk for HCC is not recommended. (LoE 4, strong recommendation) (Pro 29, Against 2, Abstain 0)

Recommendation 8. Routine use of CEUS for staging of HCC is not recommended. (LoE 2, strong recommendation) (Pro 31, Against 0, Abstain 0)

CEUS FOR CHARACTERIZATION OF FOCAL LIVER LESIONS

Before starting liver CEUS, it is necessary to review the patient's clinical history, laboratory data and any prior imaging. The entire liver and the FLL should be interrogated using conventional B-mode and color Doppler US to obtain reproducible information regarding segmental localization, size and relation to vessels and other anatomic landmarks, as well as to guarantee optimal examination quality and ascertain whether underlying cirrhosis is present. The range of tumor types differs between cirrhotic and non-cirrhotic livers, with description of the characterization of FLL discussed separately for each.

Recommendation 9. Before performing CEUS to characterize FLLs, it is recommended that a systematic liver examination be performed using B-mode and Doppler US. (LoE 5, strong recommendation) (Pro 32, Against 0, Abstain 0)

Characterization of FLLs in the non-cirrhotic liver

The probability of an FLL being benign (including inflammatory) or malignant depends on the symptoms and past medical history. An incidentally detected FLL in otherwise healthy and asymptomatic persons is likely benign (Linhart et al. 1998; Hirche et al. 2002), whereas with pre-existing malignant disease, the probability of malignancy is

significantly higher (Albrecht et al. 2004). In patients with supportive symptomatology, FLLs may raise suspicion for phlegmonous inflammation or abscess formation.

The primary aim of CEUS in patients with a non-cirrhotic liver is to differentiate benign from malignant FLLs (Karhunen 1986; Volk et al. 2001; Dietrich et al. 2004, 2005, 2006, 2007; Strobel et al. 2008, 2009, 2011; Seitz et al. 2009, 2010, 2011; Trillaud et al. 2009; Bernatik et al. 2010; Devine et al. 2010; Trojan et al. 2010; von Herbay et al. 2010; Guang et al. 2011; Xie et al. 2011; Martie et al. 2012; Sporea et al. 2012, 2014; Sandrose et al. 2016). Thus, CEUS is useful in facilitating the clinical decision as to whether a sonographically detected liver lesion requires further investigation or surgery (Bartolotta et al. 2009).

Recommendation 10. CEUS is recommended as the first-line imaging technique for the characterization of incidentally detected, indeterminate FLLs at US in patients with a non-cirrhotic liver and without a history or clinical suspicion of malignancy. (LoE 1, strong recommendation) (Pro 30, Against 0, Abstain 2)

Recommendation 11. CEUS is suggested as the first-line imaging technique for the characterization of FLLs detected with US in patients with non-cirrhotic livers with a history or clinical suspicion of malignant disease. (LoE 2, weak recommendation) (Pro 31, Against 0, Abstain 0)

Recommendation 12. CEUS is recommended for the characterization of FLLs in the non-cirrhotic liver in patients with inconclusive findings at CT or MRI (LoE 2, strong recommendation) and is suggested if biopsy of the FLL was inconclusive. (LoE 5, weak recommendation). (Pro 30, Against 1, Abstain 0)

Recommendation 13. CEUS is recommended for characterization of FLLs in the non-cirrhotic liver if both CT and MRI are contraindicated. (LoE 5, strong recommendation) (Pro 32, Against 0, Abstain 0)

For differential diagnosis of FLL, CEUS is superior to CT and equivalent to MR imaging (Dietrich et al. 2006; Seitz et al. 2009, 2010, 2011; Friedrich-Rust et al. 2013). CEUS has been shown to be the most cost-effective imaging modality in some countries in Europe (Westwood et al. 2013).

Benign solid FLLs

In addition to contrast enhancement of the FLL compared with the adjacent tissue, vascular architecture during AP can further characterize FLLs. The enhancement patterns are summarized in Table 2.

Hemangioma. After focal fatty sparing, hemangioma is the second most common benign solid lesion of the liver (Hirche et al. 2002; Kaltenbach et al. 2016). In

Table 2. Enhancement patterns of benign focal liver lesions in the non-cirrhotic liver

Lesion	Arterial phase	Portal venous phase	Late phase	Post-vascular phase
Hemangioma				
Typical features	Peripheral nodular enhancement	Partial/complete centripetal fill-in	Incomplete or complete enhancement	Iso-/slightly hypo-enhancing
Additional features	Small lesion: complete, rapid centripetal enhancement		Non-enhancing regions	Non-enhancing regions
Focal nodular hyperplasia				
Typical features	Hyper-enhancing from the center, complete, early	Hyper-enhancing	Iso-/hyper-enhancing	Iso-/slightly hyper- or hypo-enhancing
Additional features	Spoke-wheel arteries Feeding artery	Un-enhanced central scar	Un-enhanced central scar	
Hepatocellular adenoma				
Typical features	Hyper-enhancing, complete	Iso-enhancing	Iso-enhancing	
Additional features	Non-enhancing regions	Hyper-enhancing Non-enhancing regions	Slightly hypo-enhancing Non-enhancing regions	
Focal fatty infiltration				
Typical features	Iso-enhancing	Iso-enhancing	Iso-enhancing	Iso-enhancing
Focal fatty sparing				
Typical features	Iso-enhancing	Iso-enhancing	Iso-enhancing	Iso-enhancing
Abscess				
Typical features	Peripheral enhancement, no central enhancement	Hyper-/iso-enhancing rim, no central enhancement	Hypo-enhancing rim, no central enhancement	Hypo-enhancing rim
Additional features	Enhanced septa Hyper-enhanced liver segment	Hypo-enhancing rim Enhanced septa Hyper-enhanced liver segment		
Simple cyst				
Typical features	Non-enhancing	Non-enhancing	Non-enhancing	Non-enhancing

asymptomatic patients with a normal-appearing liver on US and without findings or history of malignant or chronic liver disease, a well-circumscribed, round-shaped hyper-echoic and homogeneous FLL <30 mm without intra-lesional vessels at color Doppler and without halo sign is diagnostic of hemangioma. CEUS or other contrast-enhanced imaging modalities are not recommended for further characterization (Dietrich et al. 2013; Vidili et al. 2019). CEUS is indicated when a definitive diagnosis of a hemangioma cannot be achieved using conventional US, as the addition of CEUS markedly improves the diagnostic accuracy in 90%−95% of cases (Dietrich et al. 2007; Strobel et al. 2008; Trillaud et al. 2009).

The typical CEUS feature of a hemangioma is peripheral, discontinuous nodular (globular) enhancement in the AP with progressive centripetal partial or complete fill-in (Foschi et al. 2010; Sienz et al. 2011; Cui et al. 2013; Chiorean et al. 2015a). Complete fill-in occurs only in 40%−50% of cases during the LP. This fill-in is often more rapid in smaller lesions, and the entire lesion may be hyper-enhancing in the AP. Persistent iso- or hyper-enhancement is sustained through the LP (Lamuraglia et al. 2006; Dietrich et al. 2007, 2019; Hirche et al. 2007; Sienz et al. 2012; Inoue et al. 2016). On post-vascular imaging using Sonazoid, hemangiomas appear iso- to hypo-enhancing relative to the surrounding liver parenchyma, and may resemble metastatic tumors and HCCs (Little et al. 1991; Sugimoto et al. 2014). The overall sensitivity of CEUS for diagnosis of hemangioma is 86% (95% CI: 81%−92%) according to a meta-analysis including 612 cases from 20 studies (Friedrich-Rust et al. 2013).

Atypical appearances, particularly LP hypo-enhancement (UCA washout) or lack of centripetal fill-in, have been described and may be explained by the destruction of microbubbles that are not adequately replenished because of very long bubble transit times within the lesion (Chiorean et al. 2015a). Hemangiomas with arteriovenous shunts (also called high-flow or shunt hemangiomas) exhibit rapid homogeneous hyper-enhancement in the AP and, therefore, can be confused with focal nodular hyperplasia (FNH) or even hepatocellular adenoma (HCA) or HCC (Dietrich et al. 2007). They are almost always hyper-enhancing in the PVP and LP. Thrombosed hemangiomas exhibit a lack of enhancement and can be confused with malignancy if only identified during the later CEUS phases (Dietrich et al. 2007; Klinger et al. 2019).

Focal nodular hyperplasia. On CEUS, an FNH typically appears as a hyper-enhancing homogeneous lesion in all phases. The hyper-enhancement might be only mild during the PVP and LP (Dietrich et al. 2005, 2018d; Strobel et al. 2009; Piscaglia et al. 2010b, 2010c; Pei et al. 2013). Hyper-enhancement is usually marked in the AP (Pei et al. 2013), with a rapid fill-in from the center outward (a spoke-wheel pattern) (70%) or sometimes with an eccentric vascular or multilocular arterial supply (30%) (Dietrich et al. 2005; Cui et al. 2013). A centrally hypo- or non-enhancing located scar may be seen in the LP. This, together with the direction of filling of the lesion in the AP, if recognizable (centrifugal vs. centripetal), is an important feature in distinguishing FNH from shunt (high-flow) hemangiomas. In distinction to FNH, hepatocellular adenomas and hyper-vascular malignant FLLs exhibit washout as the most important CEUS feature (Dietrich et al. 2019).

In the vast majority of cases (93.5%), iso-enhancement or only slight hyper-enhancement of FNH is observed in the PVP compared with the surrounding liver parenchyma, whereas in the remainder (6.5%), hypo-enhancement is observed (Jones et al. 1992; Lee et al. 2018).

The overall sensitivity of CEUS in the diagnosis of FNH is 88% (95% CI: 81%−94%) according to a large meta-analysis of 365 cases FNH from 18 studies (Friedrich-Rust et al. 2013). Several studies have suggested that the diagnostic accuracy of CEUS for diagnosis of FNH is a "matter of size", with accuracy decreasing in patients with lesion size >30 mm (Claudon et al. 2013a, 2013b).

Hepatocellular adenoma. HCA is a rare, benign and sometimes estrogen-dependent hepatic neoplasm. Typical imaging characteristics of HCAs are displayed in smaller lesions <50 mm (Dietrich et al. 2005, 2019). At CEUS, HCA exhibits homogeneous arterial hyper-enhancement, typically with rapid, complete, peripherally dominated filling without a spoke-wheel pattern and without a peripheral globular enhancement pattern, which often enables the correct differential diagnosis, except in telangiectatic and inflammatory HCAs (Foschi et al. 2010). However, HCCs and hyper-enhancing metastases may exhibit a similar arterial enhancement pattern, making the differentiation impossible during the AP. In the early PVP, HCAs usually become iso-enhancing or, more rarely, remain slightly hyper-enhancing (Dietrich et al. 2005; Piscaglia et al. 2010b). Previous bleeding episodes or necrotic portions exhibit intratumoral non-enhancing areas in larger HCA. In most cases, washout occurs in the LP, requiring biopsy to exclude malignancy (Dietrich et al. 2019). Because of the different subtypes of HCA, characterization and differentiation (*e.g.,* from FNH and HCCs, such as the inflammatory subtype) may be difficult using CEUS as well as MRI, and biopsy (HCA <50 mm) or surgery (≥50) is indicated for final diagnosis (Lamuraglia et al.

2006). Liver-specific contrast-enhanced MRI may be helpful when HCA is suspected at CEUS to exclude multilocularity. No studies are available for the diagnosis of HCA using Sonazoid.

Focal fatty change. Focal fatty changes, either by fat infiltration or fatty sparing, usually appear on conventional B-mode US as oval or polygonal areas located along the portal bifurcation or close to the hepatic hilum and gallbladder. On visualization of possible focal fat infiltration, atypical location or history of malignancy should prompt further characterization to exclude malignant lesions. Focal fatty change exhibits the same degree of enhancement (iso-enhancing) as the surrounding liver parenchyma during all phases (Hirche et al. 2007; Janica et al. 2013). Typically, a centrally located artery can be identified (Hirche et al. 2007; Dietrich and Jenssen 2012; Dietrich et al. 2013).

Infection. The CEUS findings in phlegmonous inflammation are variable. During the early stage of infection, lesions often appear hyper-enhancing, while mature lesions develop non-enhancing foci as liquefaction progresses. Mature liver abscesses on CEUS exhibit enhancement of the margins and frequently of the septae in the AP, which sometimes can be followed by PVP hypo-enhancement. The most prominent feature on CEUS is the non-enhancement of the liquefied portions combined with arterial rim enhancement (Biecker et al. 2003; Catalano et al. 2004, 2007; Liu et al. 2008; Anderson et al. 2009). Diffuse hyper-enhancement of the affected liver subsegment(s) in the AP and LP washout of liver parenchyma surrounding the non-enhancing necrotic area have been described in the majority of cases (Anderson et al. 2009).

The appearance of granulomas and focal tuberculosis on CEUS varies, which makes it hard and sometimes impossible to differentiate these from malignancy (Liu et al. 2008; Cao et al. 2010; Dietrich et al. 2015, 2018a, 2018b, 2018c, 2018d).

Other solid benign liver lesions

A range of other, very rare, solid benign liver lesions can be seen including the following entities:

- *Active hemorrhage* (including spontaneous, traumatic and iatrogenic liver bleedings) appear as contrast extravasation, whereas *hematomas* appear as non-enhancing areas.
- *Inflammatory pseudotumor* is a rare disease whose definite diagnosis is usually made only at surgery. It may exhibit arterial enhancement and LP hypo-enhancement, falsely suggesting malignancy.
- *Hepatic angiomyolipoma* is a rare benign mesenchymal tumor. It appears homogeneous in most cases and strongly hyper-echogenic at baseline US. CEUS reveals arterial hyper-enhancement (Dietrich et al. 2007; Wang et al. 2010).
- *Cholangiocellular adenomas* (CCAs or bile duct adenomas) are rare lesions that are usually small (90% <1 cm). CEUS may reveal strong arterial hyper-enhancement and early washout in the PVP and LP (they lack portal veins), falsely suggesting malignancy (Ignee et al. 2009b; Corvino et al. 2015).
- *Hepatic epithelioid hemangioendotheliomas (HEHEs)* often manifest as multinodular FLLs. On CEUS, HEHEs exhibit rim-like or heterogeneous hyperenhancement in the AP and hypo-enhancement in the PVP and LP, a sign of malignancy (Cui et al. 2014b; Dong et al. 2016; Klinger et al. 2019). Some patients exhibit centrally located un-enhanced areas. In contrast, all hemangiomas and FNH exhibit hyper- or iso-enhancement in the PVP and LP, which is their most distinguishing feature.

For liver trauma we refer to the recently published EFSUMB Guidelines and Recommendations for the Clinical Practice of Contrast-Enhanced Ultrasound (CEUS) in Non-Hepatic Applications: Update 2017 (Sidhu et al. 2018a, 2018b).

Malignant solid FLLs

In patients with a non-cirrhotic liver, metastases are more common than primary liver malignant tumors, though conventional US is occasionally helpful in detecting the malignant nature of an FLL, by demonstrating a hypo-echoic halo and infiltration of intrahepatic vessels. Contrast-enhanced imaging is necessary to determine the malignant nature in many circumstances, which is true for US, CT and MRI (Lu et al. 1990; Dietrich et al. 2006). Contrast washout in the PVP and LP is the most important feature to determine malignancy (Claudon et al. 2013a, 2013b). Almost all metastases exhibit this feature, regardless of the enhancement pattern in the AP. Very few exceptions to this rule have been reported, mainly in liver metastases of neuroendocrine tumors and atypical HCC (Table 3).

Hepatocellular carcinoma in the non-cirrhotic liver. Hepatocellular carcinoma is the most common primary liver malignancy, and most of the patients at risk have known or unknown liver cirrhosis (Forner et al. 2012). There are few articles on the value of CEUS in the diagnosis of HCC in the non-cirrhotic liver. Generally, the enhancement patterns of HCC in the non-cirrhotic liver on CEUS are similar to those of HCC in the cirrhotic liver, but the size at the time of diagnosis tends

Table 3. Enhancement patterns of malignant focal liver lesions in the non-cirrhotic liver

Tumor	Arterial phase (10−30 s)	Portal venous phase (20−120 s)	Late phase (120−300 s)	Post vascular phase (>10 min)
Metastasis				
Typical features	Rim enhancement	Hypo-enhancing	Hypo-/non-enhancing	Hypo-/non-enhancing
Additional features	Complete enhancement Hyper-enhancement Non-enhancing regions	Non-enhancing regions	Non-enhancing regions	Non-enhancing regions
Hepatocellular carcinoma				
Typical features	Hyper-enhancing	Iso-enhancing	Hypo-/non-enhancing	Hypo-/non-enhancing
Additional features	Non-enhancing regions	Non-enhancing regions	Non-enhancing regions	Non-enhancing regions
Cholangiocarcinoma				
Typical features	Rim-like hyper-enhancement, central hypo-enhancement	Hypo-enhancing	Hypo-/non-enhancing	Hypo-/non-enhancing
Additional features	Non-enhancing regions Inhomogeneous hyper-enhancement	Non-enhancing regions	Non-enhancing regions	Non-enhancing regions

to be larger (Linhart et al. 1998). HCA and FNH are the main differential diagnoses (Zheng et al. 2014; Dietrich et al. 2019). HCCs in the non-cirrhotic liver are usually hyper-enhancing in the AP, typically with a chaotic vascular pattern (Hayashi et al. 2016), and variably iso- or hypo-enhancing in the PVP and LP (Inoue et al. 2016). Hyper-enhancement in the AP is often homogenous but starts predominantly along the periphery (Goto et al. 2012). The fibrolamellar variant of HCC has a non-specific appearance at CEUS. According to expert opinions and case reports, these exhibit rapid wash-in with a heterogeneous pattern in the AP and early PVP and early and marked washout thereafter (Mandry et al. 2007; Arita et al. 2011a).

Cholangiocarcinoma (ICC). ICC is the second most common primary malignant liver tumor and usually arises in healthy liver parenchyma. The different treatment approaches and prognoses necessitate that ICC be distinguished from HCC (Galassi et al. 2013). Although rarely observed in Europe and America, ICC is more frequently seen in Asia, where combined HCC−ICC also exists (Dong et al. 2018).

In distinction to the late enhancement on CECT or CEMRI, ICC exhibits a variety of patterns in the AP at CEUS, but all show washout in the LP (Xu et al. 2006; Chen et al. 2008; Wang et al. 2010). The typical pattern of malignancy is better revealed by CEUS than by CECT or CEMRI (Schellhaas et al. 2018a, 2018b).

There is controversy over the differential diagnosis of HCC and ICC with CEUS (Little et al. 1991; Laghi et al. 2010; Leoni et al. 2010; Zech 2011; Barreiros et al. 2012; Dietrich et al. 2012a, 2012b, 2012c; Frydrychowicz et al. 2012; Kim et al. 2017; Kono et al. 2017; Piscaglia et al. 2017; Wilson et al. 2018). Compared with HCCs, ICCs exhibit less intense enhancement in the AP and early (<60 s) and marked washout compared with the typically late and mild washout in HCCs (Little et al. 1991). ICCs can be subcategorized into three types: mass-forming periductal infiltrating and intraductal growing. Mass-forming ICCs can exhibit four enhancement patterns in the AP: peripheral irregular rim-like enhancement, heterogeneous hyper-enhancement, homogeneous hyper-enhancement and heterogeneous hypo-enhancement (Chen et al. 2008; Wang et al. 2010). Mass-forming ICCs usually exhibit washout in the PVP and invariably marked hypo-enhancement in the LP, followed by complete hypo-enhancement in the post-vascular phase (Hatanaka et al. 2008a, 2008b; Xu et al. 2012).

During the AP, periductal infiltrating ICCs appear heterogeneously enhancing, and intraductal growing ICCs exhibit homogeneous hyper-enhancement in most cases. Both lesions exhibit marked washout during the PVP and LP (Xu et al. 2012).

Metastases. Liver metastases are the most common malignant lesions of the liver, arising mainly from cancers of the gastrointestinal tract, breast, pancreas or lung. Compared with conventional US, CEUS markedly improves the detection of liver metastases. Liver metastases can be detected and characterized reliably as hypo-enhancing lesions during the PVP and LP, with few exceptions. Washout is of marked degree and with early onset, usually before 60 s after UCA injection. In the LP, very small metastases may be conspicuous, and lesions that were occult on B-mode US can be detected (Dietrich et al. 2006). Because of the lack of Kupffer cells, metastatic lesions on post-vascular phase imaging with Sonazoid are clearly demarcated and completely hypo-enhancing (Hatanaka et al. 2008a, 2008b; Zech 2011; Frydrychowicz et al. 2012; Dietrich et al. 2012a, 2012b, 2012c; Ying et al. 2012).

Metastases usually exhibit at least some contrast enhancement in the AP and, sometimes, marked and chaotic enhancement. Rim or halo enhancement is often seen (Claudon et al. 2013a, 2013b).

Lymphoma. Lymphoma exhibits variable arterial enhancement but characteristic fast and marked washout in the PVP and LP, predictive of malignancy (Foschi et al. 2010; Heller and Gorg 2013; Trenker et al. 2014).

Focal cystic liver lesions (benign and malignant)

Focal cystic liver lesions (FCLLs) represent a wide spectrum of benign and malignant disease (Corvino et al. 2015). Benign FCLLs include simple cysts, hematomas and hemorrhagic hepatic cysts (Zhang et al. 2009; Corvino et al. 2017); abscesses, bilomas and hydatid cysts (Vachha et al. 2011); cystic cavernous hemangiomas (Cha et al. 2008); and cystic HCAs and other rare entities (Barreiros et al. 2014; Chiorean et al. 2015b). Malignant FCLLs include cystic HCCs (Lin et al. 2009), cystic lymphoma, cystic metastases as typically seen in neuroendocrine tumors (Mork et al. 2007) and other rare entities.

Simple cysts are completely non-enhancing on CEUS. CEUS is not indicated for assessment of simple cysts but is useful in evaluating complicated or atypical cysts (Corvino et al. 2017).

With complex cystic masses, CEUS characterizes the vascular flow within septa in cystadenoma and cystadenocarcinoma (Albrecht et al. 2004; Piscaglia et al. 2010b). Such septa are often visualized by US but not by CT and MRI. Some atypical cystic lesions may have a solid appearance at conventional US, thus mimicking a malignant lesion, particularly a cystic metastasis or biliary cystadenocarcinoma (Albrecht et al. 2004; Barr et al. 2018).

On CEUS, the distinguishing feature in the differential diagnosis of hepatic cystadenoma (HBCA) from hepatic cystadenocarcinoma (HBCAC) is the honeycomb septal hyper-enhancement during the AP for HBCA and the hypo-enhancement during the PVP and LP for HBCAC (Albrecht et al. 2004).

Recommendation 14. If CEUS has definitively characterized a benign FLL, further investigations are not recommended to confirm the diagnosis. (LoE 1, strong recommendation) (Pro 26, Against 0, Abstain 5)

Recommendation 15. CEUS can be used to characterize hepatic abscess in the appropriate clinical setting. (LoE 2, weak recommendation) (Pro 24, Against 1, Abstain 2)

CEUS FOR CHARACTERIZATION OF FLLS IN LIVER CIRRHOSIS

Study procedure

In addition to the general recommendations for the study of FLLs, important aspects should be followed if the liver is cirrhotic. As the AP is crucial in characterization of FLLs in cirrhosis, good visualization of the nodule is important. Despite the use of a low mechanical index (MI), microbubbles can be disrupted and acoustic output power should then be reduced, while maintaining sufficient signal intensity to allow contrast persistence until the very LP (beyond 3−4 min), crucial for detecting washout and establishing a diagnosis of HCC. Furthermore, when the arterial/early PVP is complete (after 60 s), it is recommended that the lesion is imaged intermittently (usually brief scan every 30−60 s), rather than continuously, to minimize microbubble destruction, which may cause problems in the identification of subtle or late washout.

Image interpretation and evaluation

The key feature for the diagnosis of HCC in liver cirrhosis is APHE, followed by late-onset mild washout (>60 s after injection) (Dietrich et al. 2018c; Lyshchik et al. 2018; Rodgers et al. 2019; Kono et al. 2020; Wang et al. 2020). This pattern of washout in an HCC is seen in more than 97% of cases according to a large retrospective series (Terzi et al. 2018). Arterial hyper-enhancement is usually homogeneous and intense in HCCs but may be inhomogeneous in larger nodules (>5 cm) that are necrotic. Rim enhancement is atypical for HCC. Washout is observed overall in about half the cases of HCC, but rarely in small nodules (20%−30% in those 1−2 cm, 40%−60% in those 2−3 cm) (Forner et al. 2008; Leoni et al. 2010; Sangiovanni et al. 2010). Washout is observed more frequently in HCCs with poorer grades of differentiation than in well-differentiated HCCs, which tend to be iso-enhancing in the LP (Fan et al. 2006; Jang et al. 2007; Iavarone et al. 2010; Boozari et al. 2011). ICC risk is increased in patients with liver cirrhosis, but only 1%−2% of newly detected FLLs in a cirrhotic liver are ICCs (Wildner et al. 2015; Dong et al. 2018).

Hypo-enhancement in the LP is usually less marked in HCCs than in other primary tumors or in liver metastases (Chen et al. 2006; Boozari et al. 2011). Furthermore, the washout tends to start later in HCC, usually not before 60 s after injection (Chen et al. 2006; Boozari et al. 2011) and appearing only after 180 s in up to 25% of cases (Chen et al. 2006; Boozari et al. 2011); consequently, it is important to observe nodules in cirrhosis until late (>4 min). Early washout (<60 s) has been reported to occur in poorly differentiated HCCs or to

suggest a non-hepatocellular malignancy (Chen et al. 2006; Fan et al. 2006; Jang et al. 2007; Boozari et al. 2011), most often a peripheral ICC. For details regarding the CEUS Liver Imaging Reporting and Data System (LI-RADS) classification, we refer to the published literature (Dietrich et al. 2016; Kim et al. 2017; Kono et al. 2017; Piscaglia et al. 2017; Schellhaas et al. 2017, 2018a, 2018b; Lyshchik et al. 2018; Wilson et al. 2018; Wang et al. 2020). The sensitivity of CEUS in the diagnosis of HCCs is 88% (95% CI: 84%–92%) according to a meta-analysis including 1333 HCCs from 19 studies (Friedrich-Rust et al. 2013).

Recommendation 16. CEUS can be utilized as the first line in characterization of FLLs found in patients with liver cirrhosis to establish a diagnosis of malignancy (CEUS LR-M) or, specifically, HCC (CEUS LR-5), but CT or MR imaging is required for accurate staging unless contraindicated. (LoE2, weak recommendation) (Pro 29, Against 0, Abstain 0)

Recommendation 17. CEUS can be utilized when CT or MR imaging is inconclusive, especially in FLLs in cirrhotic liver not suitable for biopsy, to assess the probability that a lesion is an HCC. (LoE3, weak recommendation) (Pro 29, Against 0, Abstain 0)

Recommendation 18. CEUS can be utilized for the selection of FLL(s) in a cirrhotic liver to be biopsied when they are multiple or have different contrast patterns. (LoE4, weak recommendation) (Pro 28, Against 0, Abstain 1)

Recommendation 19. CEUS can be used to monitor changes in enhancement patterns in FLLs in cirrhotic liver requiring follow-up. (LoE4, weak recommendation) (Pro 29, Against 0, Abstain 0)

CHARACTERIZATION OF PORTAL VEIN THROMBOSIS

CEUS is superior to color Doppler US for the diagnosis of portal vein thrombosis (Tarantino et al. 2006). Acute bland thrombus is typically "avascular" and appears as a void within the enhancing liver in all phases of CEUS but is best visualized during the PVP. A "tumor-in-vein" has the same enhancement characteristics as the tumor from which it originated, including rapid APHE and washout (Rossi et al. 2006, 2008; Tarantino et al. 2006; Ueno et al. 2006; Song et al. 2010; Dănilă et al. 2011; Raza et al. 2014; Chammas et al. 2019).

Differential diagnosis between partially occlusive/re-canalized bland thrombus and "tumor-in-vein" is more challenging. For reliable differentiation, careful assessment of the time of arrival of the UCA at the vein is needed. Early arrival of UCA at the lesion in the portal vein at about the same time as opacification of hepatic arteries suggests tumor but this behavior is not specific to HCCs. Tumors in peripheral portal veins may be mistaken for tumor nodules, erroneously downstaging the patient. Avoidance is facilitated by real-time imaging while sweeping through the liver, especially in the PVP, to depict the tubular configuration of the tumor and its continuity with more central portal or hepatic veins.

The tumor source of a malignant portal vein thrombus may be obvious, or it may be identified with the assistance of CEUS. A suspicious thrombus within the portal vein may be amenable to US guided biopsy, targeting, if possible, any enhancing regions within the thrombus (Rossi et al. 2006; Tarantino et al. 2006; Sorrentino et al. 2009; Raza et al. 2014).

Recommendation 20. CEUS is recommended for differentiation between benign and malignant portal vein thrombosis. (LoE 2, strong recommendation) (Pro 26, Against 0, Abstain 0)

CONTRAST-ENHANCED INTRA-OPERATIVE US

Several studies using different UCAs have reported that contrast-enhanced intra-operative US (CE-IOUS) enhances tumor detection and allows assessment of the region for resection, where previously a pre-treatment colorectal liver metastasis was present but has regressed (Torzilli et al. 2004, 2007, 2014; Leen et al. 2006; Fioole et al. 2008; Nakano et al. 2008; Arita et al. 2011a, 2011b; Huf et al. 2017). In particular, CE-IOUS has proven valuable for the differential diagnosis between HCC and dysplastic nodule, using both SonoVue (Torzilli et al. 2007) and Sonazoid (Arita et al 2011a). In addition, CE-IOUS may have a significant impact on surgical strategy depending on the attitude of the surgeon (Jones et al. 2012). The study procedure and image interpretation of CE-IOUS examination are the same as for the transabdominal approach described earlier in this article (Torzilli et al. 2004). The most important difference is that CE-IOUS is performed during the surgical procedure and uses an intra-operative transducer, which, because of its higher frequency, may require a higher UCA dosage.

Recommendation 21. CE-IOUS can be used to detect and characterize FLLs not detected at pre-operative

imaging. (LoE 3, strong recommendation) (Pro 27, Against 0, Abstain 0)

Recommendation 22. CE-IOUS is recommended for assessment of the region for resection, where previously a pre-treatment colorectal liver metastasis was present but has regressed. (LoE 2, strong recommendation) (Pro 27, Against 0, Abstain 0)

CEUS FOR GUIDING BIOPSY

Ultrasound is an established technique for guiding biopsy of FLLs, with an excellent safety profile and good overall accuracy (Lorentzen et al. 2015a, 2015b; Sidhu et al. 2015). Ultrasound is inferior to MR and CT in detecting liver lesions, but the sensitivity of CEUS is comparable with that of CECT and CEMRI; importantly, CEUS enables real-time guidance of the biopsy procedure. The addition of CEUS could potentially increase the diagnostic outcome of percutaneous biopsies for four different reasons (Bang et al. 2000; Skjoldbye et al. 2002; Schlottmann et al. 2004; Wu et al. 2006; Yoon et al. 2010; Park et al. 2015; Sparchez et al. 2015; Eso et al. 2016; Kang et al. 2017, 2018; Francica et al. 2018a, 2018b; Nolsoe et al. 2018; Cao et al. 2019):

- Biopsies can be taken from perfused areas to avoid necrosis or avascular tissue (Bang et al. 2000; Wu et al. 2006; Sparchez et al. 2015; Eso et al. 2016; Francica et al. 2018a, 2018b; Nolsoe et al. 2018; Cao et al. 2019).
- Biopsies can be taken of poorly visualized or "invisible" lesions on B-mode US (Skjoldbye et al. 2002; Schlottmann et al. 2004; Yoon et al. 2010; Park et al. 2015; Sparchez et al. 2015; Kang et al. 2017, 2018; Nolsoe et al. 2018; Cao et al. 2019).
- Biopsy can be avoided completely if a CEUS study unequivocally reveals typical features of benign FLL or HCC in an appropriate patient population (Claudon et al. 2013a, 2013b).
- The combination of image fusion techniques and CEUS may have a synergistic effect on both modalities. CEUS fusion has been proven to visualize lesions invisible by conventional US fusion in a substantial number of cases (Kang et al. 2017, 2018).

Study procedure

Depending on the contrast agent, a two-step procedure is recommended. Typically, the first UCA dose is injected to characterize the target lesion and select a zone for biopsy; the second dose used for the CEUS-guided biopsy itself. Dual-screen contrast imaging is recommended with simultaneous contrast imaging on one side to visualize the lesion and conventional B-mode imaging on the other side to track the needle. Biopsy should be performed during the contrast phase in which the lesion is best visualized. CEUS before a suggested US-guided biopsy of an FLL can help by avoiding biopsy in the case of a diagnostically unequivocal CEUS result. Conventional un-enhanced US guidance is adequate for biopsy of most tumors detected on real-time US, and there is no rationale for substituting CEUS guidance for routine use.

Recommendation 23. CEUS guidance should be attempted to biopsy FLLs that are invisible or inconspicuous at B-mode imaging. (LoE 1, strong recommendation) (Pro 27, Against 0, Abstain 2)

Recommendation 24. CEUS guidance should be considered for FLLs with potential necrotic areas or if previous biopsy resulted in necrotic material. (LoE 4, weak recommendation) (Pro 29, Against 0, Abstain 0)

INTRACAVITARY USES

Intracavitary CEUS (ICCEUS, intracavitary administration of UCAs) is increasingly used as an adjunct to US-guided interventional techniques (Cui et al. 2015, 2016; Lorentzen et al. 2015a, 2015b; Yusuf et al. 2018). Concepts and techniques have been published (Heinzmann et al. 2012; Ignee et al. 2013, 2016). Liver abscess drainage and biliary drainage procedures using ICCEUS have been described in detail. A systematic review covering the role of CEUS in relation to percutaneous intervention has been published (Nolsoe et al. 2018).

Study procedure

The standard dosage for intracavitary CEUS is approximately 1 drop of UCA per 10 mL of normal saline but may vary with the anticipated distribution volume (*e.g.,* ascites). Higher concentrations are possible for problem-solving decisions, but accurate imaging is dependent on correct dilution dosage; high concentrations will result in acoustic shadowing. Higher-frequency transducers (linear, endoscopic US) demand higher concentrations.

CEUS-guided biliary interventions

CEUS-guided percutaneous cholangiography can delineate the biliary tree *via* drainage catheters or T-tubes placed intra-operatively or during endoscopic access (Zuber-Jerger et al. 2008; Ignee et al. 2009a, 2015; Xu et al., 2009, 2012; Mao et al. 2010; Zheng et al. 2010; Chopra et al. 2012; Luyao et al. 2012; Velosa et al. 2013; Daneshi et al. 2014; Urade et al. 2014). Intraoperatively, 3-D intracavitary CEUS can aid the surgeon

in planning resection lines (Zuber-Jerger et al. 2008; Ignee et al. 2009a, 2015; Xu et al., 2009; Mao et al. 2010; Zheng et al. 2010; Chopra et al. 2012; Luyao et al. 2012; Velosa et al. 2013; Daneshi et al. 2014; Urade et al. 2014).

ICCEUS of the biliary tree is used during the intervention procedure

- to demonstrate puncture or cannulation success
- to evaluate for communication with other structures, for example, intestine (Velosa et al. 2013), pleural cavity (Ignee et al. 2009a, 2009b, 2015), gallbladder, vessels (Daneshi et al. 2014) and abscesses
- to evaluate the level of obstruction (Luyao et al. 2012) and after the interventional procedure
- to evaluate for dislodgement or occlusion

Importantly, intracavitary CEUS reduces or obviates radiation exposure during the intervention. In addition, it has a positive impact on patient logistics during both the procedure and follow-up by making transport of the patient to an X-ray fluoroscopy room unnecessary when catheter dislodgement is suspected, allowing bedside investigation with a portable US system.

CEUS for the abscess drainage

Image-guided liver abscess management, normally with US or CT guidance, is a standard procedure, with the advantages of both efficiency and effectiveness, allowing percutaneous abscess drainage with either a needle or a catheter, with concurrent lavage (Lorentzen et al. 2015a, 2015b). During image-guided intervention, correct placement of the needle or the drainage catheter can be confirmed using intracavitary CEUS (Ignee et al. 2016). Communication with other abscess cavities or other structures can be revealed or excluded (*e.g.,* bile duct, pancreatic pseudocyst, peritoneal cavity, pleural space), resulting in additional interventions in a number of instances (biliary drainage, pleural drainage, additional abscess interventions in complex cases, pseudocyst intervention, *etc.*). During follow-up, the cavity size can be evaluated, and dislodgement of a drainage catheter can be identified or excluded (Girlich et al. 2011; Muller et al. 2015).

Recommendation 25. ICCEUS can be used for delineation of the liver abscess cavity and identification of correct drain position and of communication with other structures. (LoE 3, weak recommendation) (Pro 28, Against 0, Abstain 1)

Recommendation 26. ICCEUS can be used to guide transhepatic biliary interventions. (LoE 3, weak recommendation) (Pro 27, Against 1, Abstain 1)

CEUS FOR INTERVENTIONAL TUMOR ABLATION

Ultrasound is the most commonly used imaging modality for guiding ablation therapies in patients with liver tumors (Lencioni and Crocetti 2012; Liu et al. 2018). US allows real-time precise placement of the ablation needle in any visualized target lesion. The procedure is tolerable, rapid and cost-effective in comparison to other imaging modalities, allowing positioning within the target in a short time (Lorentzen et al. 2015a, 2015b). The adjunctive use of CEUS is recommended for pre-treatment evaluation of the ablation target and for peri-procedural assessment of treatment results (Lorentzen et al. 2015a, 2015b; Nolsoe et al. 2018). CEUS-Guided ablation of liver tumors may be dispensed with when the lesion target is well recognizable at conventional B-mode US.

Pre-treatment CEUS

Pre-treatment evaluation includes assessment of ablation target size, vascularization and tumor margins. For ablative treatment of undetected or inconspicuous target lesions at un-enhanced US, availability of CEUS-guided technology and possibly real-time CEUS fusion imaging is of pivotal importance (Liu et al. 2011; Chan et al. 2015; Park et al. 2015; Bo et al. 2016; Francica et al. 2018a, 2018b). Often, two intravenous injections are required: the first to identify the target lesion and plan treatment, the second for correct positioning of the ablation needle. For CEUS, a dual screen is recommended to allow the simultaneous real-time visualization of the probe insertion with both conventional B-mode US and CEUS.

Recommendation 27. CEUS before US-guided ablation procedure is recommended as a complement to US, CT and MRI for treatment planning. (LoE 2, strong recommendation) (Pro 27, Against 0, Abstain 2)

Recommendation 28. CEUS guidance is recommended for the US-guided ablation of tumors that are invisible or inconspicuous on US. (LoE 2, strong recommendation) (Pro 27, Against 0, Abstain 2)

Performance of CEUS 10−15 min after ablation treatment should be considered for immediate evaluation of therapeutic efficacy and for early detection of residual viable tumor, which allows for instantaneous CEUS-guided re-ablation under the same anesthesia. This technique has been proven to decrease both the number of second ablation

sessions and the tumor recurrence rate during follow-up (Meloni et al. 2012; Mauri et al. 2014; Xu et al. 2019). Similarly, CEUS fusion imaging with CT/MRI for peri-procedural assessment of ablation has been reported to enable immediate repeat ablations under CEUS or CEUS-CT/MR fusion imaging guidance and to decrease long-term local tumor progression (Numata et al. 2012; Zhong-Zhen et al. 2012; Li et al. 2016; Makino et al. 2016; Ye et al. 2019).

Study procedure

After cessation of ablation, a 5- to 10-min period is necessary before performing CEUS to allow the hyperechoic "cloud" of gas produced during the ablation to diffuse into tissue. In cases of residual tumor, a second CEUS injection must be used to allow correct insertion of the ablation needle.

Recommendation 29. CEUS is recommended for evaluation of the treatment effect after ablation and guidance for immediate US-guided re-treatment of residual tumor. (LoE 2, strong recommendation) (Pro 26, Against 2, Abstain 0)

Post-treatment CEUS

CEUS is a reliable method for evaluation of the ablation margin and detection of tumor recurrence, potentially reducing the number of CT examinations needed during follow-up (Choi et al. 2003; Kisaka et al. 2006; Minami et al. 2007; Lencioni and Llovet 2010; Frieser et al. 2011; Zhong-Zhen et al. 2012; Zheng et al. 2013; Qu et al. 2013; Xu et al. 2019; Ye et al. 2019).

Follow-up CEUS

The purpose of first post-ablation CEUS is to evaluate immediate treatment response of the target lesion (by size, perfusion, safety margin and residual viable tumor) and to look for complications (such as hemorrhage, hepatic infarction, bile duct dilation, abscess, biliary tumor, *etc.*) (Chen et al. 2004; Meloni et al. 2012). Regular CEUS follow-up weeks to months after ablation can detect local recurrence and new lesions (Frieser et al. 2011; Liu et al. 2011; Bo et al. 2016; Francica et al. 2018a, 2018b; Nolsoe et al. 2018). Frequently, more than one injection is required to evaluate multi-ablated lesions, any suspicious areas or new lesions.

Recommendation 30. CEUS is recommended as the priority imaging method in the follow-up after ablation treatment to identify residual or recurrent tumor at appropriate time intervals. (LoE 2, strong recommendation) (Pro 24, Against 0, Abstain 3)

In the early post-ablation evaluation (within the first 30 d), a thin, uniform enhancing hyperemic rim is visible along the periphery of the necrotic region, similar to the findings on CECT. Due attention must be paid to avoid confusing this with recurrence.

MONITORING MEDICAL TUMOR TREATMENT RESPONSE

Neo-angiogenesis is an important target for novel anti-cancer treatments and many new anti-angiogenesis or anti-vascular treatments aim at destroying or limiting the growth of tumor vessels (Ferrara and Kerbel 2005; Kessler et al. 2010). Dynamic CEUS (DCEUS) has emerged for monitoring the response to these drugs (Dietrich et al. 2012a). Initially, such monitoring relied on qualitative analyses only. More recently, robust and quantitative features have been developed. To achieve successful results, standardization and strict control of scanner settings are needed (Dietrich et al. 2012a).

Methodology and equipment for quantification

Measurements of contrast kinetics are performed using a time−intensity curve (TIC) analysis of dynamic contrast enhancement. Background subtraction is necessary to compensate for attenuation effects (Bos et al. 1995) and extract reliable time-based features, such as time to peak and mean transit time. However, the nonlinear compression applied to the original signals (required to display them on video monitors) distorts amplitude-based TIC features (*e.g.*, peak intensity and area under the curve) (Peronneau et al. 2010). The majority of reports have used uncompressed, post-beamformed data (radiofrequency data are not required because the phase information is not essential). TICs based on such raw data sets allow for accurate assessment of both time-based and amplitude-dependent features. All manufacturers that supply built-in analysis packages on their scanners use this type of data, but off-line software packages are also available (Cosgrove and Lassau 2010). For details on the administration of UCA and quantitative analysis, we refer to the EFSUMB position paper (Dietrich et al. 2012a).

Assessment of anti-angiogenic treatment

Because antiangiogenic treatments frequently induce necrosis without causing tumor shrinkage, functional imaging techniques are particularly suitable for the early assessment of response, a task for which both the RECIST and World Health Organization (WHO) size criteria (World Health Organization 1979; Therasse et al. 2000) are unsatisfactory. Studies of various types of tumors, such as HCC, gastrointestinal stromal tumor (GIST) and renal cell carcinoma, treated with anti-angiogenic

therapies have confirmed that DCEUS may allow early prediction of response to treatment (De Giorgi et al. 2005; Lamuraglia et al. 2006; Lassau et al. 2006, 2010, 2011, 2012, 2017; Lencioni et al. 2006; Seitz 2010; Frampas et al. 2013; Hudson et al. 2015, 2018; Lazar et al. 2014; Lo et al. 2016; Wu et al. 2017; Klinger et al. 2019). The first multicenter study including more than 500 patients in 19 centers (Lassau 2014) correlated DCEUS with progression-free survival (PFS) and overall survival (OS). A 40% decrease in the area under the curve at 1 mo was correlated to PFS and OS in patients treated with thyrosine kinase inhibitors (O'Connor et al. 2017).

Recommendation 31. DCEUS can be used in the quantitative assessment of response to targeted therapies in patients with malignant tumors of the liver. (LoE 2, weak recommendation) (Pro 22, Against 0, Abstain 5)

Pediatric liver lesions

US imaging is the ideal imaging technique for many areas in pediatrics and should be the first-line imaging modality whenever practicable (Sidhu et al. 2017). The advantages of US are established: it is child-friendly, easy to use in the difficult child and repeatable and has limited safety issues. Moreover, in liver imaging, the relatively fat-free body habitus of the child renders US an ideal technique for assessment of FLLs. CEUS in the assessment of pediatric liver lesions has been investigated by a number of groups, predominantly in Europe and almost exclusively using the agent SonoVue, with some reports from North America using Definity; these agents were used off-label in children. The FDA has approved the use of *Lumason* in the assessment of FLLs in children. This is likely to increase the use of CEUS as a first-line imaging method for the incidental FLL, as well as for the assessment of malignancy, recurrence and treatment response, in the pediatric population (Jacob et al. 2013).

Experience with the assessment of pediatric FLL has been based on the extensive investigations of adult FLL, with initial experience using SonoVue in pediatric practice centered mainly around the investigation of indeterminate FLLs seen on an US examination (Jacob et al. 2013). A single study applying adult criteria to the CEUS diagnosis of FNH and HCA found good concordance with MRI and CT imaging (Fang et al. 2019). More extensive experience has been documented with blunt abdominal trauma of the liver and in the follow-up of focal areas of injury in the liver (Valentino et al. 2008; Menichini et al. 2015; Durkin et al. 2016). Experience using CEUS in the assessment of liver transplant recipients is limited, with studies reporting success mainly with areas of infarction and abscess formation, with vascular "Doppler rescue" useful (Bonini et al. 2007; Rennert et al. 2012; Torres et al. 2019). For details we refer to the EFSUMB position paper Role of Contrast-Enhanced Ultrasound (CEUS) in Paediatric Practice: An EFSUMB Position Statement (Sidhu et al. 2017).

Safety and dose

The most extensive assessment of safety in children has been with *SonoVue*, with reports of severe anaphylaxis in 1 of 137 patients (0.6%) studied (Piskunowicz et al. 2015) and two minor delayed adverse reactions in 2 of 305 patients (0.7%) in a review of local clinical practice (Yusuf et al. 2017). Current evidence suggests that the safety profile of SonoVue use in children is similar to that in adults.

The FDA-recommended dose for Lumason in assessing FLL is based on weight, 0.03 mL/kg, not exceeding 2.4 mL per injection. On a more practical basis, other authors have indicated a dose regime for the liver that is age based, with adult doses for children >12 y of age (SonoVue 2.4 mL), half the adult dose between 6 and 12 y (1.2 mL) and one-quarter the adult dose under the age of 6 y (0.6 mL), well within the safety margins of dose-finding studies in adults (Yusuf et al. 2017). These relatively small doses may continue to decrease as imaging technology improves (Sidhu et al. 2017).

Indications for pediatric liver CEUS

- The child with any incidentally discovered FLLs on US examination should also have the opportunity to be assessed with CEUS. The CEUS examination requires an intravenous line, as would a CECT or CEMRI examination. Limited evidence suggests that the CEUS assessment of a FLL is as accurate in the child as in the adult, without the morbidity of ionizing radiation, iodinated contrast or gadolinium-based contrast or the need for sedation or general anesthesia.
- Any indeterminate FLL in a child with underlying chronic liver disease from any cause on a follow-up program should be examined by CEUS before any other imaging, so that further imaging is avoided if the lesion is categorically benign.
- The assessment of vascular complications after liver transplantation benefits from the "Doppler rescue" of a CEUS examination before resorting to a CT examination.
- Initial investigation of blunt abdominal trauma in children should involve a CT examination except for the most trivial trauma. Follow-up of the identified areas of localized, low-energy liver trauma may be readily performed with a CEUS examination, where a complicating traumatic pseudoaneurysm is readily identified and progressive healing of

lacerations or hematomas can be recorded on serial investigations.

Recommendation 32. CEUS assessment of FLLs in children is consistent with findings in the adult patients, and it should be used to characterize these lesions. (LoE 2b, strong recommendation) (Pro 25, Against 0, Abstain 0)

Recommendation 33. CEUS follow-up of traumatic liver injuries in children should be utilized for the assessment of complications, reducing ionizing radiation exposure (LoE 2, strong recommendation) (Pro 26, Against 0, Abstain 1)

DOCUMENTATION

All US examinations should principally be documented both by wording and by image storage to ensure high-quality patient care (American Institute of Ultrasound in Medicine 2020). However, there exists little scientific evidence to substantiate how this should be done. This is a matter of expert opinion and practice differs substantially worldwide. Each image lesion should be described in terms of size, localization (liver segment) and contrast enhancement in all phases (Piscaglia et al. 2012). The operator should record the temporal behavior and degree of enhancement relative to surrounding tissue (non-enhanced, hypo-enhanced, iso-enhanced or hyper-enhanced), as well as the UCA distribution (homogeneous or heterogeneous) (Dietrich et al. 2018b).

The written report must include type and dose of UCA applied. Furthermore, the enhancement pattern in all phases should be described with a conclusion regarding diagnosis and follow-up. It is important to report washout timing in actual seconds or minutes. Real-time video clips should be recorded, preferably digitally, in a format which enables later retrieval and comparison (Stenman et al. 2013). The clips should ideally show the whole examination, but at least the AP and other clinically relevant parts of the scan should be recorded and stored. Cine loops can be supplied with still images of relevant findings. Finally, the clips and images should be archived permanently.

Recommendation 34. The user of a CEUS examination should report the type and dose(s) of contrast agent, the enhancement pattern and clinically relevant findings in a written format. (LoE 5, strong recommendation) (Pro 27, Abs 1, Against 0)

Recommendation 35. During the CEUS examination representative images and cine loops should be captured and stored according to the relevant medical-legal framework. (LoE 5, strong recommendation) (Pro 26, Abs 0, Against 2)

CLINICAL TRAINING AND EDUCATION

Adequate knowledge and hands-on training are prerequisites for building competence in the use of CEUS. Therefore, it is of great importance to maintain high-quality education and high professional standards in the practice of CEUS. In 2006, three levels of training requirements were defined by EFSUMB (Lencioni et al. 2006), with Appendix 14 specifically addressing the use of CEUS (Seitz 2010). It is recommended that CEUS should be performed by operators who have obtained adequate expertise with both conventional US and CEUS. They should be familiar with these techniques and the distribution of pathologies within their local medical environment; they should be recognized as competent by local standards and the relevant medicolegal framework. Some federations offer dedicated CEUS courses on a regular basis, often in collaboration with the UCA- or US-equipment industry, and it is beneficial for any user of CEUS to attend such educational activities (Gilja 2009). It is advised that investigators intending to start using CEUS attend relevant courses and spend time under the supervision of an expert. Ideally, their own department should have a sufficient volume of examinations to maintain adequate numbers of cases with various pathologies. Furthermore, it is advised that the manufacturers are consulted to maintain up-to-date CEUS scanner software. The practice of CEUS also requires knowledge of UCA administration, contra-indications and necessary skills to handle possible side effects within the medicolegal framework of the country of practice.

Recommendation 36. Users must have adequate knowledge and training in CEUS, UCA administration and contraindications, and perform the examination within the relevant medico-legal framework. (LoE 5, strong recommendation) (Pro 27, Against 0, Abstain 1)

ERRORS AND ARTIFACTS IN CEUS OF THE LIVER

Errors may occur in CEUS of the liver because of the limitations of CEUS and other factors, such as contrast dose, mechanical index, image artifacts, background noise, pseudo-enhancement, unintended microbubble destruction, attenuation, shadowing and prolonged heterogeneous liver enhancement. These errors may result in lesion mis-characterization. It is recommended that CEUS imaging interpretation should be performed in

conjunction with analysis of the patient's clinical history, symptoms and laboratory values. In select cases when CEUS imaging results are discordant, correlation with other imaging modalities or tissue sampling might be advised.

Recommendation 37. Appropriate dose of contrast agent based on lesion location, patient factors and sensitivity of the US scanner, as well as imaging with an appropriate low mechanical index, should be used to produce high-quality CEUS images. (LoE 5, strong recommendation) (Pro 26, Against 0, Abstain 2)

Similar to every other imaging modality, image artifacts are often encountered in liver CEUS (Dietrich et al. 2011, 2014; Fetzer et al. 2018). They may be intrinsic to contrast-mode imaging itself or relate to traditional B-mode artifacts. Some artifacts may affect image quality or simulate pathology but rarely result in misdiagnosis (Cui et al. 2014a, 2014b). Others may be useful, leading to a more confident diagnosis.

Recommendation 38. When using CEUS, a knowledge of artifacts associated with CEUS is recommended. (LoE 5, strong recommendation) (Pro 27, Against 0, Abstain 1)

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